IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

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SANOFI-AVENTIS and DEBIOPHARM, S.A.

SANOFI-AVENTIS U.S. LLC, SANOFI-AVENTIS, DEBIOPHARM, S.A., Plaintiffs, v. SANDOZ, INC., Defendant.	)	CIVIL ACTION NO.:

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Sanofi-Aventis U.S. LLC, Sanofi-Aventis and Debiopharm, S.A. (hereinafter "Plaintiffs"), by way of Complaint against Sandoz, Inc. allege as follows:

THE PARTIES

1. Sanofi-Aventis is a corporation organized and existing under the laws of France, having its principal place of business at 174 avenue de France, Paris, France. Sanofi-Aventis is a global innovator healthcare company whose core therapeutic areas are oncology, diseases of the central nervous system, cardiovascular disease, and internal medicine.

2. Sanofi-Aventis U.S. LLC is the U.S. subsidiary of Sanofi-Aventis, and is a limited liability company organized and existing under the laws of the state of Delaware, having commercial headquarters at 55 Corporate Drive, Bridgewater, New Jersey 08807.

3. Debiopharm, S.A. ("Debiopharm") is a corporation, existing under the laws of Switzerland, having its principal place of business at Forum "après-demain" Chemin Messidor 5-7, Case postale 5911, CH - 1002 Lausanne, Switzerland. Debiopharm develops innovative and life-saving pharmaceuticals.

4. On information and belief, Defendant Sandoz, Inc. ("Sandoz") is a corporation, incorporated and existing under the laws of the State of Colorado, and having a principal place of business at 506 Carnegie Ctr., Ste. 400, Princeton, New Jersey 08540.

5. On information and belief, Sandoz is in the business of developing, manufacturing, marketing, and distributing generic pharmaceutical products, which are copies of products invented and developed by innovator pharmaceutical companies.

6. On information and belief, Sandoz assembled and caused to be filed with the United States Food and Drug Administration ("FDA"), pursuant to 21 U.S.C. § 355(j),

Abbreviated New Drug Application No. 78-817, concerning a proposed generic drug product, oxaliplatin solution for injection in 50 mg vial (5 mg/ml) and 100 mg vial (5 mg/ml) formulations.

JURISDICTION AND VENUE

7. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

8. Sandoz is subject to personal jurisdiction in New Jersey because it regularly and systematically conducts business within New Jersey, has an office within New Jersey, and sells various products throughout the United States, including within New Jersey.

9. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b), (c) and 28 U.S.C. § 1400(b).

COUNT 1
INFRINGEMENT OF U.S. PATENT NO. 5,338,874

10. Plaintiffs repeat and reallege paragraphs 1-9 above as if fully set forth herein.

11. Sanofi-Aventis U.S. LLC holds approved new drug application ("NDA") 21-759 for Eloxatin®, the active ingredient of which is oxaliplatin. Eloxatin® is approved for the treatment of colorectal cancer. There are no generic oxaliplatin products approved by the FDA for sale in the United States.

12. Debiopharm is the owner of United States Patent No. 5,338,874 ("the '874 patent") (attached as "Exhibit A"). Sanofi-Aventis is the exclusive licensee of the '874 patent.

13. On information and belief, Sandoz submitted to the FDA ANDA No. 78-817 under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use and sale of injectable oxaliplatin formulations.

14. On information and belief, Sandoz submitted its ANDA No. 78-817 to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its generic oxaliplatin solution before the expiration of the '874 patent.

15. Sandoz made, and included in its ANDA, a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, the '874 patent is invalid and not infringed, and sent notice of that certification pursuant to 21 U.S.C. § 355(j)(2)(B) to Plaintiffs.

16. By filing its ANDA No. 78-817 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its proposed drug products before the expiration of the '874 patent, Sandoz committed an act of infringement under 35 U.S.C. § 271(e)(2).

17. Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Sandoz seeks approval in its ANDA will also infringe one or more claims of the '874 patent under 35 U.S.C. § 271.

18. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of the aforementioned ANDA relating to Sandoz's generic oxaliplatin products be a date which is not earlier than the expiration date of the '874 patent plus any other regulatory exclusivity to which Plaintiffs are or become entitled.

COUNT 2
INFRINGEMENT OF U.S. PATENT NO. 5,716,988

19. Plaintiffs repeat and reallege paragraphs 1-18 above as if fully set forth herein.

20. Debiopharm is the owner of United States Patent No. 5,716,988 ("the '988 patent") (attached as "Exhibit B"). Sanofi-Aventis is the exclusive licensee of the '988 patent.

21. On information and belief, Sandoz submitted its ANDA No. 78-817 to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its generic oxaliplatin solution before the expiration of the '988 patent.

22. Sandoz made, and included in its ANDA, a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, the '988 patent is invalid and not infringed, and sent notice of that certification pursuant to 21 U.S.C. § 355(j)(2)(B) to Plaintiffs.

23. By filing its ANDA No. 78-817 under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use or sale of its proposed drug products before the expiration of the '988 patent, Sandoz committed an act of infringement under 35 U.S.C. § 271(e)(2).

24. Further, the commercial manufacture, use, offer for sale, sale and/or importation of the generic oxaliplatin products for which Sandoz seeks approval in its ANDA will also infringe one or more claims of the '988 patent under 35 U.S.C. § 271.

25. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of the aforementioned ANDA relating to Sandoz's generic oxaliplatin products be a date which is not earlier than the

expiration date of the '988 patent plus any other exclusivity to which Plaintiffs are or become entitled.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request:

A. Judgment that Sandoz has infringed one or more claims of the '874 and '988 patents by filing the aforesaid ANDA relating to Sandoz's generic oxaliplatin products;

B. A permanent injunction restraining and enjoining Sandoz and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of generic oxaliplatin products as claimed in the '874 and '988 patents;

C. A declaration that the effective date of any approval of the aforementioned ANDA relating to Sandoz's generic oxaliplatin formulations be a date which is not earlier than the expiration date of the '874 and '988 patents plus any other regulatory exclusivity to which Plaintiffs are or become entitled;

D. A declaration that this case is exceptional within the meaning of 35 U.S.C. § 285 and an award of reasonable attorney fees, expenses, and disbursements of this action; and

E. Such other and further relief as the Court may deem just and proper.

Dated: June 14, 2007

Respectfully submitted,

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EXHIBIT A

US005338874A

United States Patent [19]

Nakanishi et al.

[11] Patent Number: 5,338,874

[45] Date of Patent: Aug. 16, 1994

[54] CIS OXALATO (TRANS 1-1,2--CYCLOHEXANEDIAMINE) PT(II) HAVING OPTICALLY HIGH PURITY

[75] Inventors: **Chihiro Nakanishi; Yuko Ohnishi; Junji Ohnishi; Junichi Taniuchi; Koji Okamoto; Takeshi Tozawa,** all of Kanagawa, Japan

[73] Assignee: **Tanaka Kikinzoku Kogyo K.K.,** Japan

[21] Appl. No.: **43,901**

[22] Filed: **Apr. 7, 1993**

[30] **Foreign Application Priority Data**

Jan. 12, 1993 [JP] Japan 5-019508

[51] **Int. Cl.**[5] **C07F 15/00**

[52] **U.S. Cl.** **556/137**

[58] **Field of Search** 556/137

[56] **References Cited**

PUBLICATIONS

Kidani et al., J. Med. Chem., vol. 21, No. 12, pp. 1315–1318 (1978).

Primary Examiner—JoseACU G. Dees
Assistant Examiner—Porfirio Nazario-Gonzalez
Attorney, Agent, or Firm—Klauber & Jackson

[57] **ABSTRACT**

Disclosed herein is cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) optically high purity. Because of its complete optical purity, the compound is effective as raw material of such a medicine as a carcinostatic agent. The complete optical purity of the above compound may be proved by comparing the respective melting points of the cis-oxalato (trans-1-1,2-cyclohexanediamine).

2 Claims, 1 Drawing Sheet

FIG. 1

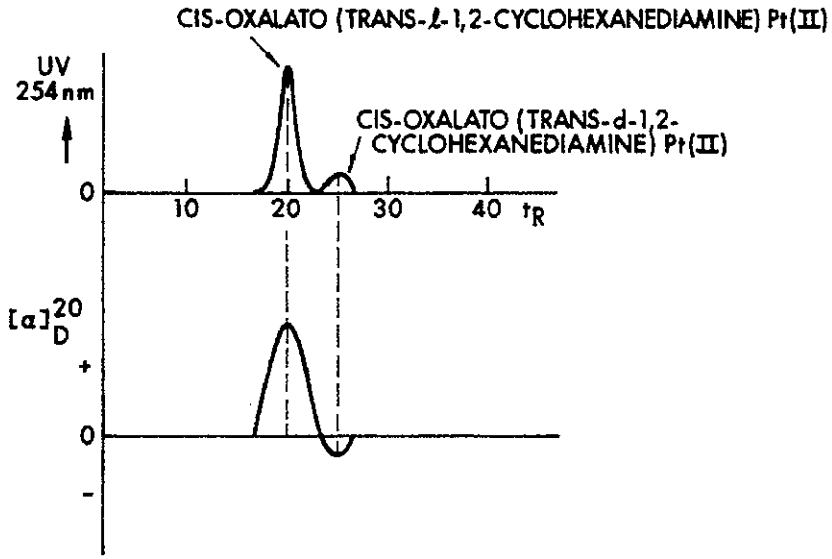
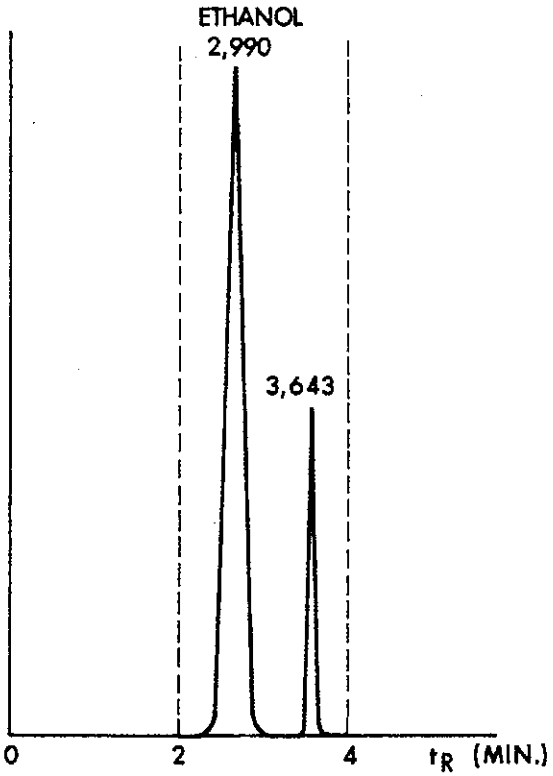


FIG. 2



GAS CHROMATOGRAM TRANS-dℓ-1,2-CYCLOHEXANEDIAMINE

CIS OXALATO (TRANS 1-1,2--CYCLOHEXANEDIAMINE) PT(II) HAVING OPTICALLY HIGH PURITY

BACKGROUND OF THE INVENTION

The present invention relates to cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically high purity which can be employed as raw material of a carcinostatic agent.

While a platinum (II) complex of 1,2-cyclohexanediamine as a platinum (II) complex exhibiting a carcinostatic activity is known, the complex is a mixture of isomers synthesized from a mixture of isomers (cis, trans-d and trans-l) existing in 1,2-cyclohexanediamine the starting material thereof.

The trans and cis isomers of the 1,2 cyclohexanediamine may be optically resoluted by means of a metal complex utilizing the difference of solubilities between the two isomers. For example, in Japanese patent publication No. 60-41077, while the cis-isomer is precipitated by adding a nickel (II) salt to such a nonaqueous solvent such pure methanol containing the two isomers, the trans-isomer is precipitated by adding the nickel salt and hydrochloric acid and aqueous sodium hydroxide. Since the trans-isomer of the nickel complex is slightly soluble in water and easily soluble in an organic solvent and the cis-isomer is slightly soluble in an organic solvent and easily soluble in water, the optical resolution can be conducted.

Although cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) was synthetically obtained through a reaction between the trans-1-1,2-cyclohexanediamine obtained in accordance with the above method and K_2PtCl_1 (Japanese patent publication No. 60-41077). This was also found to be the mixture with cis-oxalato (trans-d-1,2-cyclohexanediamine) Pt(II). No data are presented in the Japanese patent publication No. 60-41077 which confirm the optical purity of the cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) and relate to circular duchroism (CD) exhibiting its steric configuration and to an angle of rotation ($[\alpha]_D$) exhibiting its optical activity. No differences can be distinguished between their respective elemental analysis values, infrared spectra and electron spectra of the isomers mentioned in the Japanese patent publication No. 60-41077.

In the cis-oxalate (trans-1-1,2-cyclohexanediamine) Pt(II) conventionally reported, the isolation of the complex consisting of two trans-dl isomers is insufficient so that the question of the purity of the isolated Pt(II) complex remains.

Large differences in connection with a carcinostatic activity and a secondary effect between isomers of many optically active medicines, and their optical purity is especially important when they are employed as medicines.

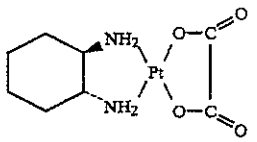
SUMMARY OF THE INVENTION

The present invention has been made in view of this standpoint.

An object of the present invention is to provide a platinum complex compound having optically high purity.

Another object of the invention is to provide a platinum complex compound which is useful as raw material of a pharmaceutically active agent because of its high purity.

The present invention is cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically high purity having a general formula of Formula (1).



(1)

The cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically high purity of the present invention may be prepared by completely and optically resoluting the Pt(II) optical isomers by means of a process of optically resoluting an optically active platinum complex compound disclose in an application of the same Applicant of the same date.

Since the complex compound of the present invention contains no cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically isomer thereof, the excellent results of acute toxicity can be obtained in comparison with cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) conventionally obtained contaminated with an optical isomer so that it is effective for providing medicines on higher safety.

The boiling point of the cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) is, because of the absence of impurities, lower than of that of conventionally prepared cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II).

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a chromatogram obtained in HPLC of cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) before optical obtained in Example 1, Example 2 and Example 3. The upper portion shows an amount of elution per unit time as a relative absorption amount of ultraviolet ray at 254 nm, and the lower portion 1 shows an amount of elution per unit time as a relative degree of rotation.

FIG. 2 is a chromatogram of trans-dl-1,2-cyclohexanediamine obtained in (1) of Example 2.

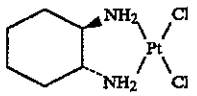
DETAILED DESCRIPTION OF THE INVENTION

The cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of optically high purity represented by Formula (1) of this invention may be prepared in accordance with a following illustrative method.

Commercially available 1,2-cyclohexanediamine (for instance, trans-1-1,2-cyclohexanediamine made by Aldrich, cis and trans-dl mixed 1,2-cyclohexanediamine made by Tokyo Kasei K.K.) may be employed. The compounds made by Aldrich and Wako Junyaku were employed without further treatment because of their relatively high purity, and the geometrical isomers of cis and trans that made by Tokyo Kasei may be resoluted and purified in accordance with such a known process as that disclosed in Japanese patent publication No. 61-4827. The optical resolution of the trans isomer may be conducted by forming a diastereoisomer in accordance with a normal method by means of tartaric acid and employing a recrystallization method.

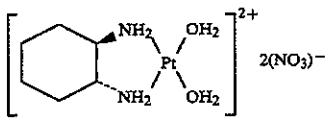
A crystal of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) represented in Formula 2 may be obtained

by a reaction between the trans-1-1,2-cyclohexanediamine previously obtained and an equivalent weight of potassium tetrachloroplatinate [K_2PtCl_4] dissolved in water at room temperature over 10 hours.



(2)

After the compound represented in Formula 2 is suspended in water followed by the addition of two equivalent weights of an aqueous solution of silver nitrate, the reaction is allowed to proceed over 24 hours in the dark followed by the removal of silver chloride by means of filtration to produce an aqueous solution of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nitrate represented in Formula 3. After potassium iodide is added to this solution followed by the removal of the excess silver ion as silver iodide by means of filtration and the decolorization and purification by active carbon, an equivalent weight of oxalic acid in respect to the potassium tetrachloroplatinate is added to produce a crude crystal of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) after the two hours' reaction. Cis-oxalato(-trans-1-1,2-cyclohexanediamine) Pt(II) obtained by the recrystallization of the said crude crystal from hot water is a mixture with cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) which is an optical isomer thereof.



(3)

Then, the recrystallized crystal is completely isolated as cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) in accordance with the process of resoluting and purifying the optically active Pt(II) isomers after the crystal is dissolved in water. That is, the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) contaminated with no optical isomers can be obtained by freeze-drying an aqueous solution separately eluted by means of high peformance liquid chromatography (hereinafter referred to as "HPLC"), for example, under the following conditions.

Separation column: 4.6 mm of inner diameter and 25 cm of height packed with OC of Daicel Chemical Industries, Ltd.

Mobile phase: othanol/methanol=30:70 (volume ratio)

Flow rate: 0.2 ml/min.

Column temperature: 40° C.

Detector:

ultraviolet ray 254 nm

optical rotation 580 nm.

the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) having the high optical purity in accordance with the present invention is active against a tumor "leukomia L1210" and effective as a carcinostatic agent.

EXAMPLES

Then, a representative process of preparing the cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) of this invention, its properties and biological activities will be described in Examples. Further, in fact, that compound prepared by a conventional method is a mixture of optical isomers will be shown contrary to a known fact.

EXAMPLE 1

① Preparation of cis-dichloro(trans-1-1,2-cyclohexanodiamine) Pt(II)

A reaction between 46.8 g of trans-1-1,2-cyclohexanediamine made by Aldrich ($[\alpha]^{19}_D = -35.6°$, 4% H_2O) and 170 g of potassium tetrachloroplatinate (made by Tanaka Kikinzoku Kogyo K.K.) in an aqueous solution at room temperature over 10 hours yielded needles of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II). Yield: 99%.

② Preparation of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nirtrate

The cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) obtained above was suspended in 1.6 liters of water to which was added two molar volumes of silver nitrate for proceeding a reaction in the dark over 24 hours, and the silver chloride produced during the reaction was filtered off. After 4.8 g of potassium iodide was added to this filtrate followed by the precipitation of the excess silver ion as silver iodide produced during the reaction of over 12 hours, 1 g of active carbon for purification and decolorization was added which was then filtered off together with the silver iodide.

③ Preparation of cis-oxalate(trans-1-1,2-cyclohexanediamine) Pt(II)

To the filtrate obtained above was added 48 g of oxalic acid dihydrate to yield 90 g of a white crude crystal after a two hours' reaction.

Then, 80 g of this crude crystal was recrystallized from three liters of hot water, and 45 g of the obtained crystal was dissolved into 9 liters of water. HPLC was conducted employing the solution under the following conditions to obtain a chromatogram of FIG. 1.

Column for optical resolution: Column having a length of 50 cm and an inner diameter of 5 cm packed with OC (Daicel Chemical Industries, Ltd., a filler prepared by adsorbing a cellulose carbamate derivative to silica gel)

Mobile phase: ethanol/methanol=30:70 (volume ratio)

Flow rate: 2.0 ml/min.

Column temperature: 40° C.

Detection:

ultraviolet ray 254 nm

optical rotation 589 nm.

The upper portion of FIG. 1 shows an amount of elution per unit time as a relative absorption amount of ultraviolet ray at 254 nm, and the lower portion of FIG. 1 shows an amount of elution per unit time as a relative degree of rotation. At a retention time (t_R) of 25 minutes, cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) was found to be contaminated. The optical purity of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) prepared by employing the trans-1-1,2-cyclohexanediamine made by Aldrich ($[\alpha]^{19}_D = -35.6°$, 4% H_2O) was calculated in accordance with a below equation to be 88.5% of an enantiomer excess rate (Table 1). Then, cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) of 100% of an optical purity (e.e.) was obtained by collecting an aqueous solution eluted in fractions from 15 minutes to 22 minutes (t_R) followed by freeze drying. Yield: 39.8 g 50% (based on the crude crystal).

[Equation for calculating optical purity]

Optical purity (%) . . . e.e (%) =

{([content of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)] − [content of [cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II)])/ ([content of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)] + [content of [cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II)])} × 100

(e.e.: enantiomer excess rate)

EXAMPLE 2

① Resolution of cis and trans geometrical isomers

To a solution prepared by dissolving 100 g of cis, trans-dl-mixed-1,2-cyclohexanediamine into 640 ml of methanol was added a solution prepared by dissolving 104 g of nickel chloride [$NiCl_2.6H_2O$] into 1760 ml of methanol which was then reacted at room temperature for 2 hours under stirring. A precipitated yellow crystal [Ni(cis-1,2-cyclohexanediamine)Cl_2 (31.6 g) was filtered and washed with methanol and air-dried. To this crystal was added 140 ml of 6-normal hydrochloric acid and then its pH was adjusted to 4.2∼4.5 with a 15% sodium hydroxide aqueous solution. After a precipitated royal purple crystal [Ni(trans-dl-1,2-cyclohexanediamine)-$(II_2O)_2Cl_2$] (72.0 g) was filtered and washed, 120 ml of 6-normal hydrochloric acid was added thereto. It was concentrated under a reduced pressure followed by addition of 600 ml of ethanol and 600 ml of acetone to obtain colorless precipitate [trans-dl-1,2-cyclohexanediamine.2HC.] (42.54 g) after filtration which was then wased with ethanol-acetone. After this was extracted with chloroform and dried with potassium carbonate, a colorless liquid [trans-dl-1,2-cyclohexanediamine (35.5 g)] ($[\alpha]^{19}_D$=0°, 4% H_2O) was obtained. A single peak appeared on a gas chromatogram at t_R=3.043 minutes.

FIG. 2 is a gas chromatogram of trans-dl-1,2-cyclohexanediamine.

The gas chromatography was conducted under the following conditions.

Column: CP-Cyclodextrin-B-236-M-19 50 m×0.25 mm (inner diameter) df=0.25 μm

Column temperature: 200° C.

Carrier gas: N_2, 2 kg/cm^2

Injector temperature: 200° C.

Detector: FID (200° C.)

Sample volume: 1 μl.

② Optical resolution of trans-dl-1,2-cyclohexanediamine

To 35.5 g of the trans-dl-1,2-cyclohexanediamine previously obtained was added 671 ml of water for dissolving under heating at 90° C. The standing thereof for 12 hours after the gradual addition of 22.10 g of d-tartaric acid and 13.4 ml of glacial acetic acid produced 16.23 g of a diastereoisomer (trans-1-1,2-cyclohoxanediamine (1) tartaric acid. This was recrystallized from water twice. No further change of the rotation of angle was observed after the repeated recrystallization as shown in FIG. 2.

After 9.23 g of the diastereoisomer obtained was dissolved into a small amount of water followed by the addition of 5.64 g of sodium hydroxide, it was extracted with ether and was distilled under a reduced pressure to obtain 3.20 g of a colorless liquid, trans-1-1,2-cyclohexanediamine.

③ Preparation of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II)

In accordance with the same procedures as those of ① of Example 1 except that the trans-1-1,2-cyclohexanediamine obtained in ② of Example 2 was employed as raw material in place of the trans-1-1,2-cyclohexanediamine made by Aldrich of ① of Example 1, 9 g of the corresponding Pt(II) complex was obtained.

④ Preparation of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nitrate

In accordance with the same procedures as those of ② of Example 1 except that the Pt(II) complex obtained in ③ of Example 2 was employed in place of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) obtained in ① of Example 1, an aqueous solution of the desired Pt(II) complex was obtained.

⑤ Preparation of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt (II)

In accordance with the same procedures as those of ③ of Example 1 except that the aqueous solution of the Pt (II) complex obtained in ④ of Example 2 was employed in place of the aqueous solution of the Pt(II) complex obtained in ② of Example 1, 7 g of a crude crystal of cis-oxalato(trans-1-1,2-cyclohexancdiamine) Pt(II) was obtained. After the recrystallization of this crude crystal from hot water was conducted, 4 g of the recrystallized crystal was dissolved into 800 ml of water. Th HPLC of this solution under the same conditions of those of ③ of Example 1 revealed that cis-oxalato(trans-d-1,2-cyclohexanediamine) Pt(II) which was an optical isomer was apparently contaminated at t_R=25 minutes as shown in FIG. 1.

The optical pority of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) synthesized by employing the raw material isolated in accordance with a process of resoluting and purifying isomers (Japanese patent application No. 61-4827) was e.e.=90.0% in accordance with the equations of ③ of Example 1 as shown in Table 1. Then, cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) of 100% of an optical purity (e.e.) was obtained by collecting an aqueous solutioneluted in fractions from 15 minutes to 22 minutes (t_R) followed by freeze drying. Yield: 3.6 g, 51% (based on the crude crystal).

EXAMPLE 3

① Preparation of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II)

In accordance with the same procedures as those of ① of Example 1 except that the trans-1-1,2-cyclohexanediamine made by Wako Junyaku K.K. ($[\alpha]^{19}_D$=34.9°, 4% H_2O) was employed in place of the trans-1-1,2-cyclohexanediamine made by Aldrich of ① of Example 150 g of the corresponding Pt(II) complex was obtained.

② Preparation of cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) anitrate

In accordance with the same procedures as those of ② of Example 1 except that the Pt(II) complex obtained in ① of Example 3 was employed in place of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) obtained in ① of Example 1, an aqueous solution of the desired cis-diaquo(trans-1-1,2-cyclohexanediamine) Pt(II) nitrate was obtained.

③Preparation of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II)

In accordance with the same procedures as those of ③ of Example 1 except that the aqueous solution of the Pt(II) complex obtained in ② of Example 3 was employed in place of the aqueous solution of the Pt(II) complex obtained in ② of Example 1, 90 g of a crude crystal of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) was obtained. After the recrystallization of this crude crystal from hot water was conducted, 45 g of the recrystallized crystal was dissolved into 9 liters of water. The HPLC of this solution under the same conditions of those of ③ of Example 1 revealed that cis-oxalato(trans-d-1,2-cyclohexanediamine) PT(II) which was an optical isomer was apparaently contaminated at t_R=25 minutes as shown in FIG. 1. The optical purity of the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) synthesized by employing trans-1-1,2-cyclohexanediamine made by Wako Junyaku K.K. as raw material was e.e.=86.8% in accordance with the equation of ③ of Example 1 as shown in Table 1. Then, cis-oxalato(trans-1-1,2 cyclohexanediamine) Pt(II) of 100% of an optical purity (e.e.) was obtained by collecting an aqueous solution eluted in fractions from 15 minutes to 22 minutes (t_R) followed by freeze drying. Yield: 39.1 g, 43% (based on the crude crystal).

COMPARATIVE EXAMPLE

For comparing and evaluating the optical purity, the physicochemical properties and the biological properties obtained in accordance with the present invention, the cis-oxalate(trans-1-1,2-cyclohexanediamine) Pt(II) was synthesized as Comparative Example by employing the raw material made by Tokyo Kasei K.K. in accordance with the following procedures disclosed Japanese patent publication No. 60-41077.

To 3 g of cis-dichloro(trans-1-1,2-cyclohexanediamine) Pt(II) was added 500 ml of water followed by the boiling thereof for dissolution. After two moles of $AgNo_3$ (2.6 g) were added and was stireed for 2 to 3 hours in the dark, the filtrations were repeated until the filtrate became transparent. After the filtrate was concentrated under a reduced pressure to 100 ml, 1.3 g of potassium oxalate was added to the concentrated solution followed by standing for 8 hours at room tempeature. The solution was again concentrated at a reduced pressue to produce white crystalline precipitate. The precipitated was recrystallized from water.

The comparisons of the optical purity between the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) of Examples and Comparative Example, that of the physicochemical properties and that of the biological properties are shown in Table 1, Table 3 and Table 4, respectively.

No difference is recognized between the compounds of Examples and Comparative Examples in connection with their properties, elemental analysis (C,H,N) and infrared spectra in Table 3. However, the melting points of the compounds of Examples 1 to 3 are lower than that of Comparative Example. This fact indicates that while the cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II) conventionally obtained is contaminated with such an impurity of its optical isomer, the cis-oxalato(-trans-1-1,2-cyclohexanediamine) Pt(II) obtained in Examples of the present invention is contaminated with no impurities.

Table 4 shows an acute toxicity test (LD_{60}) and a resistance against a tumor of L1210 of cis-oxalato(trans-1-1,2-cyclohexanediamine) Pt(II). The test was conducted by prescribing L1210 in a peritoneal cavity of six CDF_1 mice/one group (the number of transplanted cells is 10^n per mouse and prescribing the medicine in the poritoncal cavity on a first day, a fifth day and a ninth day.

TABLE 1

Optical Purity of Cis-Oxalato(Trans-1-1,2-Cyclohexanediamine) Pt(II)

Experiment	Raw Material	Optical Purity (e. e. %) Before Resolution By HPLC	→	After Resolution By HPLC
Example 1	Aldrich	88.5	→	100
Example 2	Tokyo Kasei	90.0	→	100
Example 3	Wako Junyaku	86.8	→	100
Com. Ex.	Tokyo Kasei	90.0	→	100

TABLE 2

Angle of Rotation of trans-1-1,2-cyclohexanediamine-(+)-tartaric acid

Tokyo Kasei (Lot No. FBZ01)	$[\alpha]_n^{10}$ (1% H_2O)
Before Recrystallization	+12.0+ ± 0.1°
After One Recrystallization	+12.1° ± 0.1°
After two Recrystallizations	+12.1° ± 0.1°

TABLE 3

Physicochemical Properties of cis-oxalato(trans1-1,2-cyclohexanediamine)Pt(II)

Experiment	Melting Point	CD (Δε)	$[\alpha]_n^{20}$ (0.5%, H_2O)
Example 1*	198.3~	255 nm	
Example 2*	291.7° C.	+0.67 ± 0.19	>74.5° C.
Example 3*		324 nm	
		+0.61 ± 0.10	
Comp. Ex. (JP Publi. No. 60-41077)	>300° C.	not mentioned	not mentioned

*High Purity Sample Prepared by HPLC

TABLE 4

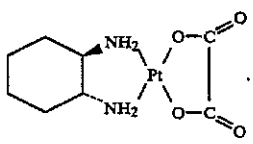
Acute Toxicity Test and Tumor Resistance Against L1210 of Cis-Oxalato(Trans-1-1,2-cyclohexamediamine) Pt(II)

Experiment	Acute Toxicity Test LD_{50}	Tumor Resistance T/C (%) (mg/kg) 25	12.5	6.25	3.12	1.56	0.78
Example 1*	18.2~20.8	T					
Example 2*	mouse IP	129P	280P (2/6)	311P (3/6)	207P	158P	132P
Example 3*							
Comp. Ex.	14.8~19.0 mouse IP	T 81	308P (4/6)	253P (1/6)	191P	158P	

*High Purity Sample Prepared by HPLC
P: Effective (Over 125%)
T: Toxic (Large Weight Loss)
(3/6): This means that three out of six was cured.

What is claimed is:

1. Optically pure cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) having a general formula of Formula (1).



(1)

2. Cis-oxalato (trans-1-1,2-cyclohexanediamine) Pt(II) as claimed in claim 1, wherein the melting point thereof is between 198° C. and 292° C.

* * * * *

EXHIBIT B

US005716988A

United States Patent [19]

Ibrahim et al.

[11] **Patent Number: 5,716,988**

[45] **Date of Patent: Feb. 10, 1998**

[54] **PHARMACEUTICALLY STABLE PREPARATION OF OXALIPLATINUM**

[75] Inventors: **Houssam Ibrahim**, Veyrier; **Rolland-Yves Mauvernay**, Lausanne, both of Switzerland

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[51] **Int. Cl.**[6] **A61K 31/28**

[52] **U.S. Cl.** **514/492**

[58] **Field of Search** 514/492

[56] **References Cited**

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Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Young & Thompson

[57] **ABSTRACT**

A pharmaceutically stable oxaliplatinum preparation for parenteral administration comprises an aqueous solution of oxaliplatinum, in a concentration of 1 to 5 mg/ml, and with a pH in the range of 4.5 to 6. The aqueous oxaliplatinum solution is advantageously provided as a ready-to-use preparation in a sealed container.

9 Claims, No Drawings

PHARMACEUTICALLY STABLE PREPARATION OF OXALIPLATINUM

This is a 371 of PCT/1B95/00614 filed Aug. 7, 1995.

The present invention is concerned with a pharmaceutically stable preparation of oxaliplatinum for administration by the parenteral route.

Oxaliplatinum (International Nonproprietary Name) is an optical isomer prepared in 1978 by Y. Kidani from a mixture of diaminocyclohexane derivatives (dach-platinum), namely the cis-oxalato complex of platinum II, from the trans-1-1,2-diaminocyclohexane or according to "Who Drug Information" vol. 1, N° 4, 1987, the (oxalato (2-)0,0') platinum from the (1R,2R)-1,2-cyclohexane-diamine-N,N'. This complex compound of platinum is known to exhibit a therapeutic activity comparable or superior to that of other known complex compounds of platinum, such as cis-platinum for example.

As the latter, oxaliplatinum is a cytostatic antineoplastic agent which can be used in the therapeutic treatment of various types of cancers and, more particularly, those of the colon, of the ovaries, of the upper respiratory tract and also epidermoid cancers and cancers of germinal cells (testicles, mediastina, pineal gland, etc.). In addition to the above-mentioned examples of the use of oxaliplatinum, one can furthermore mention colon cancers which are resistant to pyrimidines, non-small cell lung cancers, non-Hodgkin's lymphoma, breast cancers, cancers of the upper respiratory/digestive tract, malignant melanoma, hepatocarcinoma, urothelial cancers, prostate cancers, etc, and more broadly, other types of solid tumors.

At the present time, oxaliplatinum is available for preclinical and clinical trials in vials as a lyophilisate, for reconstitution, just before the administration, with injectable water or an isotonic 5% glucose solution, and dilution with a 5% glucose solution, the administration being carried out by infusion, intravenously.

However, such a dosage form implies the use of a manufacturing process (lyophilization) which is relatively complicated and expensive as well as a reconstitution step at the time of use which requires both skill and care. Furthermore, in practice, such a method has proved to carry the risk of an error being made when reconstituting extemporaneously the solution; in actual fact, it is quite common for the reconstitution from lyophilisates of injectable pharmaceutical preparations or for diluting liquid preparations, to use a 0.9% NaCl solution; the mistaken use of such a solution in the case of the lyophilized form of oxaliplatinum would be quite harmful to the active principle, which would form a precipitate (dichloro-dach-platinum derivative) with NaCl and would bring about the rapid breakdown of said product.

Thus, in order to avoid all risk of misuse of the product and to make available to the medical practitioner or the nurse an oxaliplatinum preparation which may be used without requiring the above-mentioned operations, investigations were made to obtain an injectable solution of oxaliplatinum which would be ready to use and which, furthermore, would remain pharmaceutically stable before use for an acceptable duration of time according to recognized standards, and be easier and less expensive to manufacture than lyophilisates, while exhibiting a chemical purity (absence of isomerization) and a therapeutic activity equivalent to that of the reconstituted lyophilisate. This is the objective of the present invention.

The present inventors were able to show that this objective can be attained, in a totally surprising and unexpected manner, by using as the dose form for the administration by the parenteral route, an aqueous solution of oxaliplatinum, wherein the concentration of the active principle and the pH are within well determined respective ranges and wherein the active principle is free of any acidic or alkaline agent, buffer or other additive. It has been found, in particular, that aqueous solutions of oxaliplatinum having a concentration lesser than approximately 1 mg/ml are not sufficiently stable.

Accordingly, the object of the present invention is a stable pharmaceutical preparation of oxaliplatinum for administration by the parenteral route, wherein the oxaliplatinum is disolved in water at a concentration in the range from 1 to 5 mg/ml and at a pH in the range from 4.5 to 6, the oxaliplatinum content in the preparation representing at least 95% of the initial content and the solution remaining clear, colorless and free of any precipitate after a storage of a pharmaceutically acceptable duration. This preparation is free of any other components and should, in principle, not contain more than about 2% of impurities.

Preferably, the concentration in water of oxaliplatinum is about 2 mg/ml and the pH of the solution has an average value of about 5.3.

The stability of the aqueous solution of oxaliplatinum has also been confirmed by the measurement of the specific rotatory power, which ranges from +74.5° to +78.0°.

Thus, the term "pharmaceutically stable" should also be understood as referring to the stability of the specific rotatory power of oxaliplatinum, namely the optical purity of the solution (no isomerization). Further, the "pharmaceutically acceptable duration" during which the preparation according to the invention must remain stable should be understood here as corresponding to durations generally required in the art, i.e. for example during 3 to 5 years at room temperature or at the temperature of a refrigerator.

The manufacture of the preparation according to the invention can be carried out preferably by dissolving the oxaliplatinum in water suitable for injectable preparations, with a controlled stirring if required and preheating to about 40°, followed by a filtration for making the solution clear and one or more filtrations for making the solution sterile. After filling and closing of the primary containers selected, the preparation can further be sterilized by heating in an autoclave.

Preferably, the preparation according to the invention is in the form of an aqueous solution of oxaliplatinum which is ready for use and contained in a container, which is closed hermetically.

In a particular embodiment of the invention, the preparation according to the invention is provided as a unit active dose designed for administration by infusion and containing 50 or 100 mg of oxaliplatinum in an amount of water for injectable preparations selected according to the desired concentration.

This dose is advantageously contained in a vial made of neutral glass for pharmaceutical uses, closed by a stopper of which at least the surface extending inside the vial is inert with respect to the aqueous solution of oxaliplatinum, the space between said solution and said stopper being filled, if desired, by an inert gas.

The hermetically closed vial can also be, for example, a flexible pouch for infusion, an ampoule or furthermore a constituent member of an infusion device carrying an injection micropump.

The aqueous solution of oxaliplatinum can be administered intravenously by conventional means, when desired concomitantly with other agents, therapeutically active or not, under physicochemical conditions compatible with this

platinum derivative and in accordance with practices accepted in cancer therapy.

Oxaliplatinum can be prescribed at doses ranging from 50 to 200 mg/m^2 of body surface, preferably from 100 to 130 mg/m^2 at each administration, the duration of the administration being of about 2 to 5 hours, the administrations being generally spaced apart by 3 to 5 weeks and the complete treatment comprising up to 6 to 10 administrations.

The invention will now be described in more detail with reference to the following examples concerning the injectable preparation according to the invention, its manufacture and its stability in the course of time

EXAMPLE 1

Preparation of the Aqueous Solution of Oxaliplatinum

In a thermostated container made of glass or stainless steel, there is introduced about 80% of the amount of the injectable water needed, and this water is warmed to 40° C.±5° while stirring (800–1200 rpm).

The amount of oxaliplatinum necessary for obtaining a concentration of, for example, 2 mg/ml, is weighed separately and added to the warmed water. The weighing container is rinsed thrice with injectable water, which is also added to the main mixture. The latter is further stirred at the temperature indicated during 30±5 minutes or longer if needed, until complete dissolution of oxaliplatinum. According to one version, nitrogen can be bubbled through the water to decrease its oxygen content.

The solution is then adjusted to its desired volume or weight by the addition of injectable water, and then homogenized during further 10±2 minutes (800–1200 rpm) and finally cooled to about 30° C., while still stirring. At this stage, samples of the solution are taken for carrying out the usual tests and controls and the solution is subjected to an aseptic filtration which produces a clear filtrate, in a manner known per se, and the solution is stored at 15°–30° C. before filling.

Preferably, one will use as the starting oxaliplatinum an apyrogenic product, of a pharmaceutical quality and optically pure (>99.9%), for example such as that obtained by the process patented by Tanaka K. K.

EXAMPLE 2

Packaging

The aqueous solution of oxaliplatinum, for example at a 2 mg/ml concentration, is then filled aseptically, preferably under an inert atmosphere, for example of nitrogen, into sterilized apyrogenic 50 ml glass vials.

To obtain a better stability of the aqueous solution of oxaliplatinum, one will use preferably a neutral glass of type I.

As to the stopper, one can use, for example, stoppers made of Teflon or of an elastomer based on halogenated butyls, possibly carrying an appropriate coating, in particular of a fluorinated polymer (for example of the "Omniflex" type, from Helvoet Pharma), so that at least the surface extending inside the vial be inert, with respect to the aqueous solution of oxaliplatinum.

The space between the stopper and the aqueous solution can be filled, if desired, with an inert gas, for example with nitrogen.

EXAMPLE 3

Stability Tests

Stability tests were carried out in the course of time on the aqueous solutions of oxaliplatinum obtained as described previously and stored in different containers, more particularly using two different stoppers, namely:

Stopper A:	"Omniflex"
Stopper A(N):	"Omniflex" (with a head space filled with N_2)
Stopper B:	"Grey Butyl" (with a head space filled with N_2)

The tests were carried out over 13 weeks and at several different temperatures, namely 5° C.±3° (temperature of a refrigerator), 27.5°±2.5° (ambient temperature), 40° (at 75% relative humidity) and 50° C. to produce an artificial acceleration of the phenomenon of degradation in the course of time; furthermore, the test at 27.5° was repeated in the presence of a strong light source (1100 lux).

The analytical method used is one currently practised in the art, namely high performance liquid chromatography (HPLC), for example as described in the Journal of Parenteral Drug Assoc., p. 108–109, 1979. The analysis of the peaks of the chromatogram, makes it possible to determine the content and the percentage of impurities, of which the main one was identified as being oxalic acid. Furthermore, for each test, the pH, the color and the opalescence of the solution were measured by conventional methods described in the pharmacopoeia.

The results obtained, which are summarized in the following table, demonstrate that under all the experimental conditions used, the stability of the aqueous solution of oxaliplatinum according to the invention can be considered as pharmaceutically acceptable, when considering the percentages of oxaliplatimum and those of impurities recovered, which were lower than required, even after more than 3 months of storage at 50° C. Also, the pH remained stable. Furthermore, all the solutions remained clear, colorless and free of solid particles visible with the naked eye. Finally, it was also demonstrated that the solutions remained optically pure (no isomerization), the measured rotatory power of oxaliplatinum being in the range form about +75.7° to about +76.2°, i.e. well between the limits required (+74.5° to +78.0°).

Another series of measurements at ambient temperature and at 40° C. also confirmed the stability of the aqueous solution of oxaliplatinum over a period in excess of 10 months.

TABLE

Test ref. (stopper)	Storage conditions (°C.)	Oxaliplatimtm recovered (% of initial)	Impurities (%)	pH
A	5 ± 3	101.0	0.18	5.35
A(K)	"	101.0	0.28	5.35
B	"	100.0	0.28	5.34
A	27.5 ± 2.5	100.0	0.29	5.37
A(N)	"	100.0	0.31	5.33
B	"	100.5	0.31	5.36
A	27.5/1100 lux	100.5	0.34	5.34
A(N)	"	99.5	0.42	5.29
B	"	100.0	0.40	5.37
A	40 (75% RH)	100.0	0.35	5.45
A(N)	"	100.5	0.35	5.50
B	"	99.5	0.63	5.47
A	50	99.5	0.49	5.57
A(N)	"	99.0	0.54	5.65
B	"	99.0	1.16	5.59

We claim:

1. A pharmaceutically stable preparation of oxaliplatinum for the administration by the parenteral route, consisting of

a solution of oxaliplatinum in water at a concentration of 1 to 5 mg/ml and having a pH of 4.5 to 6, the oxaliplatinum content in the preparation being at least 95% of the initial content and the solution remaining clear, colorless and free of precipitate after storage for a pharmaceutically acceptable duration of time.

2. A preparation according to claim 1, in which the concentration of oxaliplatinum is of about 2 mg/ml of water and the pH of the solution has an average value of about 5.3.

3. A preparation according to claim 1, in which the solution of oxaliplatinum has a specific rotatory power in the range from +74.5° to +78.0°.

4. A preparation according to claim 1, in the form of an aqueous solution of oxaliplatinum ready to be used and contained in a hermetically sealed container.

5. A preparation according to claim 4, characterized in that said container contains an active unit dose of 50 to 100 mg of oxaliplatinum, which can be administered by infusion.

6. A preparation according to claim 4, characterized in that said container is a glass vial for pharmaceutical use and is closed with a stopper of which, at least, the surface extending inside the vial is inert with respect to said solution.

7. A preparation according to claim 4, characterized in that said container is a flexible pouch for infusion or an ampoule.

8. A packaged pharmaceutical product comprising a glass vial closed with a stopper, said vial containing a pharmaceutically stable preparation of oxaliplatinum consisting of a solution of oxaliplatinum in water at a concentration of 1 to 5 mg/ml and having a pH of 4.5 to 6, the oxaliplatinum content in the preparation being at least 95% of the initial content and the solution remaining clear, colorless and free of precipitate after storage for a pharmaceutically acceptable duration; wherein said stopper has an inner surface which is inert with respect to said solution, said vial further comprising inert gas filling a space between said solution and said stopper.

9. A pharmaceutical product comprising an infusion device having an injection micropump, and a container containing a pharmaceutically stable preparation of oxaliplatinum consisting of a solution of oxaliplatinum in water at a concentration of 1 to 5 mg/ml and having a pH of 4.5 to 6, the oxaliplatinum content in the preparation being at least 95% of the initial content and the solution remaining clear, colorless and free of precipitate after storage for a pharmaceutically acceptable duration.

* * * * *